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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03011397.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C Van Dijk

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Anmelder/Applicant(s)/Demandeur(s):

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ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Phenyl or heteroaryl amino alkane derivatives

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Phenyl or heteroaryl amino alkane derivatives

Detailed Description of Invention

Technical Field

The present invention relates to a phenyl or heteroaryl amino alkane derivatives which are useful as an active ingredient of pharmaceutical preparations. The phenyl or heteroaryl amino alkane derivatives of the present invention have IP receptor antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with IP receptor antagonistic activity.

More specifically, the phenyl or heteroaryl amino alkane derivatives of the present invention are useful for treatment and prophylaxis of urological diseases or disorders.

The compounds of the present invention are also useful for treatment of pain; hypotension; hemophilia and hemorrhage; inflammation; respiratory states from allergies or asthma, since the diseases also is alleviated by treatment with an IP receptor antagonist.

BACKGROUND ART

Prostaglandins (or prostanoids, PGs) are a group of bioactive lipid mediators generated from membrane phospholipids. They are formed from 20-carbon essential fatty acids containing 3, 4, or 5 double bonds, and carry a cyclopentane ring. They are divided into 6 main classes (D, E, F, G, H or I) by the cyclopentane ring structure. The main classes are further subdivided by subscripts 1, 2, or 3, reflecting their fatty acid precursors. PGI2 is a member of prostanoids, and it has a double ring structure and is derived from arachidonic acid. The receptor for PGI2 is a seven transmembrane G-protein coupled receptor, called prostacyclin receptor (IP). IP couples at least to Gs-type G-protein, and activates adenylate cyclase and

phospholipase C. The expression of IP is demonstrated in aorta, coronary/-pulmonary/cerebral arteries, platelets, lung, and dorsal root ganglions in addition to several other tissues.

One of the well-known actions of PGI2 on blood vessels is to cause vasodilation and hypotension. Especially in septic shock, PGI2 is produced and participates in the induction of systemic hypotension (G.D. Bottoms et al, Am J Vet Res 1982, 43(6), 999-1002). Therefore, IP receptor antagonists may prevent hypotension associated with septic shock.

Another well-known action of PGI2 on platelets is to suppress aggregation. In the IP receptor knock out mice, $FeCl_3$-induced thrombosis formation was enhanced in comparison with that in wild type mice (T. Murata et al, Nature 1997, 388, 678-682.), confirming the involvement of IP receptor in the platelet inhibition. Therefore, IP receptor antagonists may enhance the platelet activation and suppress excessive bleeding such as, but not limited to, hemophilia and hemorrhage.

PGI2 also participates in the inflammation. In the inflamed tissue, various inflammatory mediators, including prostaglandins, are produced. PGI2 is also generated and induces vasodilation to increase blood flow. This enhances vascular permeability, edema formation and leukocyte inflammation in the inflamed region (T. Murata et al, Nature 1997, 388, 678- 682.). Therefore, PGI2 receptor antagonists may be efficacious for the treatment of inflammation.

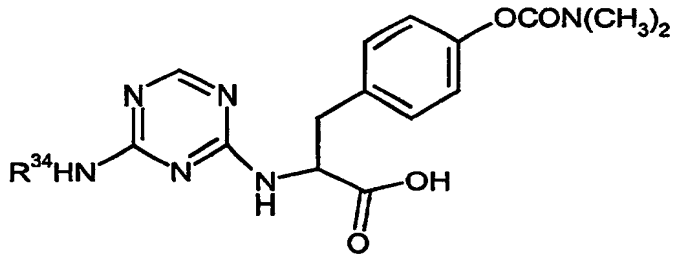
PGI2 may be involved in the pathogenesis of respiratory allergy or asthma. It is spontaneously generated and the major prostaglandin in human lung, and the appropriate antigen challenge increases PGI2 production (E.S. Schulman et al, J Appl Physiol 1982, 53(3), 589-595.). Therefore, IP antagonists may have a utility for the treatment of those respiratory diseases.

In addition, an important role of IP receptor in the induction of hyperalgesia has been clearly shown by IP receptor knockout mice (T. Murata et al., Nature 1997, 388, 678-682.). Injection of acetic acid into the peritoneal cavity induced production of PGI2. This PGI2 is considered to bind to IP receptor on sensory neurons. As IP receptor couples to the activation of both adenylate cyclase and phospholipase C, cAMP-dependent protein kinase (PKA) and protein kinase C (PKC) are activated. PKA and PKC are known to modulate ion channels on sensory neurons such as VR1, P2X3, and TTX-R. As a result, PGI2 sensitizes sensory neurons to enhance the release of neurotransmitters. An acetic acid injection induces nociceptive response (writhing) in mice and this acetic acid-induced writhing was greatly reduced in IP receptor-null mice as the same level as indomethacin-treated wild type mice. Several other in vivo hyperalgesia studies in rodents and in vitro studies further support that PGI2 plays a major role in the induction of hyperalgesia and that PGI2 acts as important modulator of sensory neurons (K. Bley et al, Trends in Pharmacological Sciences 1998, 19(4), 141-147.). Therefore, IP receptor antagonists may be useful for the treatment of pain.

Sensory neurons play very important roles not only in the pain sensation but also in the sensation of bladder distension. In normal subjects, A-delta sensory fibers are considered to play a major role to sense the bladder distention. However, in disease conditions of overactive bladder by, but not limited to, spinal cord injury, cystitis, Parkinson's disease, multiple sclerosis, previous cerebrovascular accident, and bladder outlet obstruction (BOO) caused by benign prostate hyperplasia (BPH), the sensitivity of C-fiber sensory neurons is upregulated and they contribute to the induction of the lower urinary tract symptoms. Treatment of overactive bladder patients with intravesical injection of capsaicin or its potent analog, resiniferatoxin, both of which desensitize VR1-positive C-fiber afferent neurons innervating the bladder, has been shown to be efficacious in several clinical trials (C. Silva et al, Eur Urol. 2000, 38(4), 444-452.). Therefore, C-fiber sensory neurons play an important role in the pathology of overactive bladder. PGI2 is generated locally in the bladder and it is the major prostaglandin released from the human bladder. In a rabbit BOO

model, a stable metabolite of PGI2 was reported to be increased in BOO bladder (JM. Masick et al, Prostaglandins Other Lipid Mediat. 2001, 66(3), 211-219.). Hence, PGI2 from disease bladder sensitizes C-fiber sensory neurons, and as a result, it may induce symptoms of overactive bladder. Therefore, antagonists of IP receptor are expected to be useful in the treatment of overactive bladder and related urinary disorders.

WO 00/43369 discloses pharmaceutical composition intended for the treatment of immune or inflammatory disorders represented by the general formula:



wherein

R^{34} is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl.

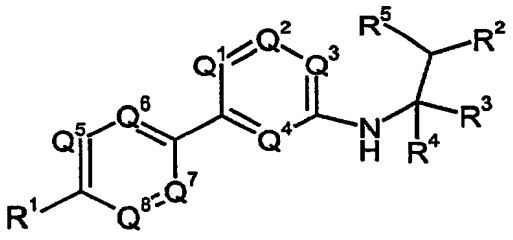
However, none of the references and other reference discloses phenyl or heteroaryl amino alkane derivatives having IP receptor antagonistic activity.

The development of a compound which has effective IP receptor antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with IP receptor antagonistic activity, has been desired.

Summary of the invention

As the result of extensive studies on chemical modification of phenyl or heteroaryl amino alkane derivatives, the present inventors have found that the compounds of the structure related to the present invention have unexpectedly excellent IP receptor antagonistic activity. The present invention has been accomplished based on these findings.

This invention is to provide a novel phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

wherein

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, $Q^7$and Q^8 independently represent CH, CR^{10} or N,

wherein

R^{10} represents halogen;

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NHR^{11}$, or $-CH_2R^{11}$,

wherein

R^{11} represents (C_{1-6}) alkyl substituted by a 3-8 membered saturated ring optionally having one or two N, (C_{2-6})alkenyl substituted by a 3-8 membered saturated ring optionally having one or two

N, or (C_{2-6})alkynyl optionally substituted by a 3-8 membered saturated ring optionally having one or two N;

R^2 represents hydrogen, hydroxy, halogen, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6 membered heteroaryl containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said aryl and heteroaryl are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, di(C_{1-6}) alkylamino, phenyl and a 5 or 6 membered heteroaryl containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaryl optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, N(C_{1-6}) alkylamino, and di(C_{1-6}) alkylamino;

R^3 represents hydrogen or C_{1-6} alkyl optionally substituted -mono, -di or -tri halogen;

R^4 represents carboxy or tetrazolyl; and

R^5 represents hydrogen, hydroxy, C_{1-6} alkyl, or C_{1-6} alkoxy.

The compounds of the present invention surprisingly show excellent IP receptor antagonistic activity. They are, therefore, suitable for the production of medicament or medical composition, which may be useful for diseases, is alleviated by treatment with an IP receptor antagonist.

More specifically, since the carboxamides derivatives of the present invention antagonize IP receptor, they are useful for treatment and prophylaxis of urological diseases or disorder.

The compounds of the present invention are also useful for treatment of urological diseases or disorders. Such diseases or disorders include bladder outlet obstruction, overactive bladder, urinary incontinence, detrusor hyper-reflexia, detrusor instability, reduced bladder capacity, frequency of micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benighn prostatic hypertrophy (BPH), prostatitis, urinary frequency, nocturia, urinary urgency, pelvic hypersensitivity, urethritis, pelvic pain syndrome, prostatodynia, cystitis, or idiophatic bladder hypersensitivity.

The compounds of the present invention are also useful for treatment of pain including, but not limited to inflammatory pain, neuropathic pain, acute pain, chronic pain, dental pain, premenstrual pain, visceral pain, headaches, and the like; hypotension;hemophilia and hemorrhage; inflammation; respiratory states from allegies or asthma, since the diseases which are alleviated by treatment with IP receptor antagonist.

Yet another embodiment of the compounds of formula (I) are those wherein:

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^3 and Q^4 represent N;

Q^1, Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^1 and Q^4 represent N;

Q^2, Q^3, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^1, Q^3 and Q^8 represent N;

Q^2, Q^4, Q^5, Q^6 and Q^7 represent CH; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^3, Q^4 and Q^8 represent N;

Q^1, Q^2, Q^5, Q^6 and Q^7 represent CH; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^1 and Q^3 represent N;

Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH;

Q^4 represent CR^{10},

wherein

R^{10} represents halogen; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^7 and Q^8 represent CH;

Q^6 represents CR^{10},

wherein

R^{10} represents halogen; and

R^4 represents carboxy.

Another embodiment of the compounds of formula (I) is those wherein:

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^6 and Q^7 represent CH;

Q^5 and Q^8 independently represent CH or CR^{10},

wherein

R^{10} represents halogen; and

R^4 represents carboxy.

Further embodiment of the compounds of formula (I) is those wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

Yet further embodiment of the compounds of formula (I) is those wherein

Q^3 and Q^4 represent N;

Q^1, Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

Further embodiment of the compounds of formula (I) is those wherein;

Q^1 and Q^4 represent N;

Q^2, Q^3, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

Further embodiment of the compounds of formula (I) is those wherein

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

Further embodiment of the compounds of formula (I) is those wherein

Q^1 and Q^3 represent N;

Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH;

Q^4 represents CR^{10},

wherein

R^{10} represents fluoro or chloro;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

Further embodiment of the compounds of formula (I) is those wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^6 and Q^7 represent CH;

Q^5 and Q^8 independently represent CH or CR^{10},

wherein

R^{10} represents fluoro or chloro;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

More preferably, said phenyl or heteroaryl amino alkane derivatives of the formula (I) is selected from the group consisting of:

N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}-4-fluorophenylalanine;
N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine;

N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}-N-[2-phenyl-1-(1H-tetraazol-5-yl)ethyl]amine;
N-{6-[4-(cyclopropylmethoxy)-2-fluorophenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopropylmethoxy)-3-fluorophenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopropylmethoxy)phenyl]-5-fluoro-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclohexylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclobutylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopentylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine;and
N-(6-{4-[2-(1-pyrrolidinyl)ethoxy]phenyl}-4-pyrimidinyl)phenylalanine.

Further, the present invention provides a medicament, which includes one of the compounds, described above and optionally pharmaceutically acceptable excipients.

Alkyl per se and "alk" and "alkyl" in alkoxy, alkanoyl, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

Cycloalkyl illustratively and preferably represent such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or adamantyl.

Aryl per se or in combination with any other term, represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms and more preferably from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl, phenanthrenyl and the like.

Heteroaryl per se or in combination with any other term, represents an aromatic mono- or bicyclic radical having generally 5 to 10 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 hetero atoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

EMBODIMENT OF THE INVENTION

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by combining various known methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by the Method [A] or [B] below.

Method [A]

(II-a) (I')

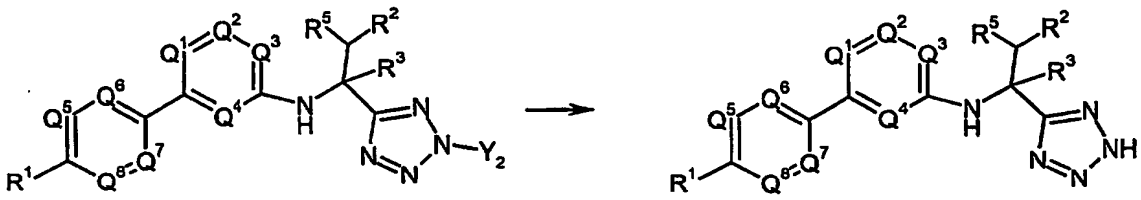
The compound of the formula (I') (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^1, R^2, R^3, and R^5 are the same as defined above) can be obtained by the hydrolysis of the compound of formula (II-a) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^1, R^2, R^3 and R^5 are the same as defined above, and Y_1 represents C_{1-6} alkyl).

The reaction can be advantageously carried out in the presence of a base including, for instance, alkali metal hydroxide such as sodium hydroxide, lithium hydroxide and potassium hydroxide; and others.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; water, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Method [B]



(II-b) (I'')

The compound of the formula (I'') (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^1, R^2, R^3, and R^5 are the same as defined above) can be obtained by the removal of Y_2 in the compound of formula (II-b) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^1, R^2, R^3 and R^5 are the same as defined above, and Y_2 represents a protecting group such as 2-(trimethylsillyl)ethoxymethyl (SEM), 2-methoxyethoxymethyl (MEM), tripheny-methyl, and the like.).

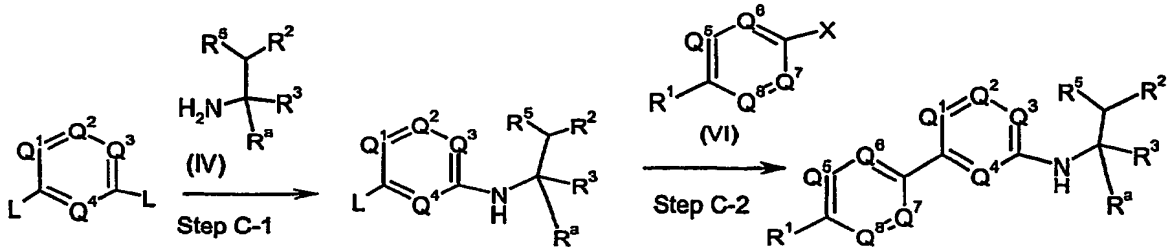
The removal of protective group Y_2 can be conducted by using a reagent including, for instance, an acid such as trifluoroacetic acid and hydrochloric acid, or tetra-butylammonium fluoride.

The reaction may be carried out without solvent or in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; alcohols such as methanol, ethanol, 1-propanol and isopropanol acetic acid, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

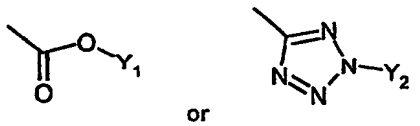
The reaction temperature can be optionally set depending on compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 60 hours and preferably 1 to 48 hours.

Preparation of the compound of intermediate

Method [C]



The compound of the formula (II) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^1, R^2, R^3 and R^5 are the same as defined above and R^a represents



can be obtained in two steps;

Step C-1: The compound of the formula (V) (wherein Q^1, Q^2, Q^3, Q^4, R^a, R^2, R^3 and R^5 are the same as defined above and L represents a leaving group including, for example, halogen atom such as chlorine, bromine, or iodine atom; and C_{1-4} alkylsulfonyloxy group, e.g., trifluoromethanesulfonyloxy, methanesulfonyloxy and the like) can be obtained by the reaction of the compound of the formula (III) (wherein Q^1, Q^2, Q^3, Q^4 and L are the same as defined) with the compound of the formula (IV) (wherein R^a, R^2, R^3 and R^5 are the same as defined above).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene;

amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction can be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, triethylamine and N,N-diisopropyl-ethylamine, dimethylaniline, diethylaniline, and others.

The reaction can be advantageously carried out in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Step C-2: The compound of the formula (II) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^1, R^2, R^3 and R^5 are the same as defined above) can be obtained by the reaction of the compound of the formula (V) (wherein Q^1, Q^2, Q^3, Q^4, R^a, R^2, R^3 and R^5 are the same as defined above) with the compound of the formula (VI) (wherein Q^5, Q^6, Q^7, Q^8, and R^1 are the same as defined above and X represents metal group including, for instance, organoborane group such as boronic acid and di-methoxy boryl; organostannyl group such as tributyl stannyl, and the like.) in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium.

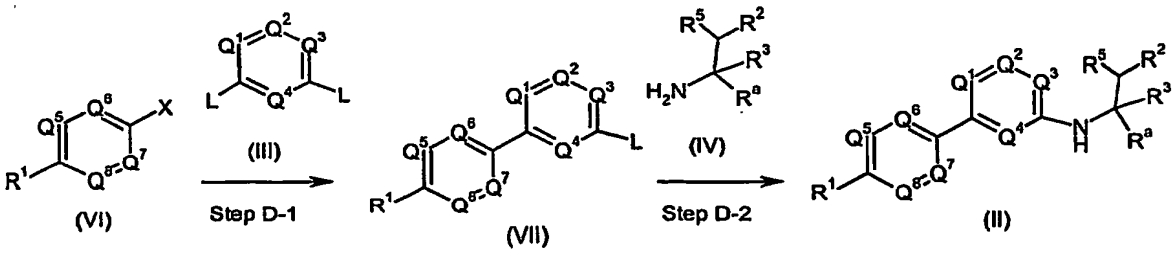
The reaction can be advantageously carried out in the presence of a base including, for instance, cesium carbonate, sodium carbonate and potassium carbonate, and the like.

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The compound of the formula (III), (IV), and (VI) are commercially available or can be prepared by the use of known techniques.

Method [D]



The compound of the formula (II) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^1, R^2, R^3 and R^5 are the same as defined above) can also be prepared in two steps;

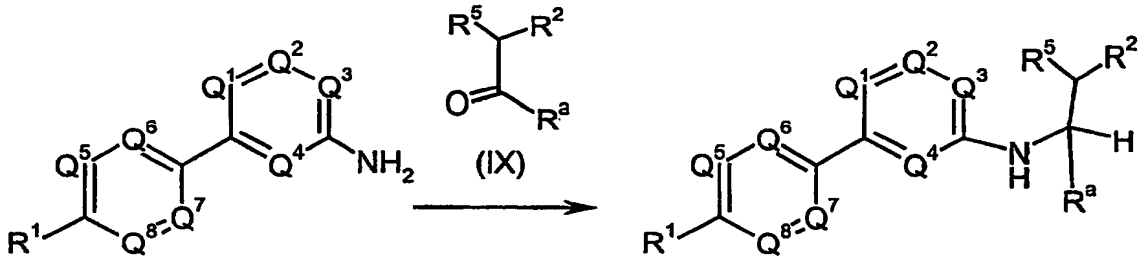
Step D-1: The compound of the formula (VII) (wherein L, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, and R^1 are the same as defined above) can be obtained by the reaction of the compound of the formula (VI) (wherein Q^5, Q^6, Q^7, Q^8, R^1 and X are the same as defined above) with the compound of the formula (III) (wherein L, Q^1, Q^2, Q^3, and

Q^4 are the same as defined above) in a similar manner described in Step C-2 of Method [C] for the preparation of the compound of the formula (II).

Step D-2 : The compound of the formula (II) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^1, R^2, R^3 and R^5 are the same as defined above) can be obtained by the reaction of the compound of the formula (VII) (wherein L, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, and R^1 are the same as defined above) with the compound of the formula (IV) (wherein R^a, R^2, R^3 and R^5 are the same as defined above) in a similar manner described in Step C-1 of Method [C] for the preparation of the compound of the formula (V).

The compound of the formula (III), (IV), and (VI) are commercially available or can be prepared by the use of known techniques.

Method [E]



(VIII) (II')

The compound of the formula (II') (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^2, and R^5 are the same as defined above) can be prepared by the reaction of the compound of the formula (VIII) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8 and R^1 are the same as defined above) with the compound of the formula (IX) (wherein R^a, R^2, and R^5 are the same as defined above) in the presence of reducing agent, for instance, such as sodium triacetoxyborohydride or sodium cyanoborohydride, and the like.

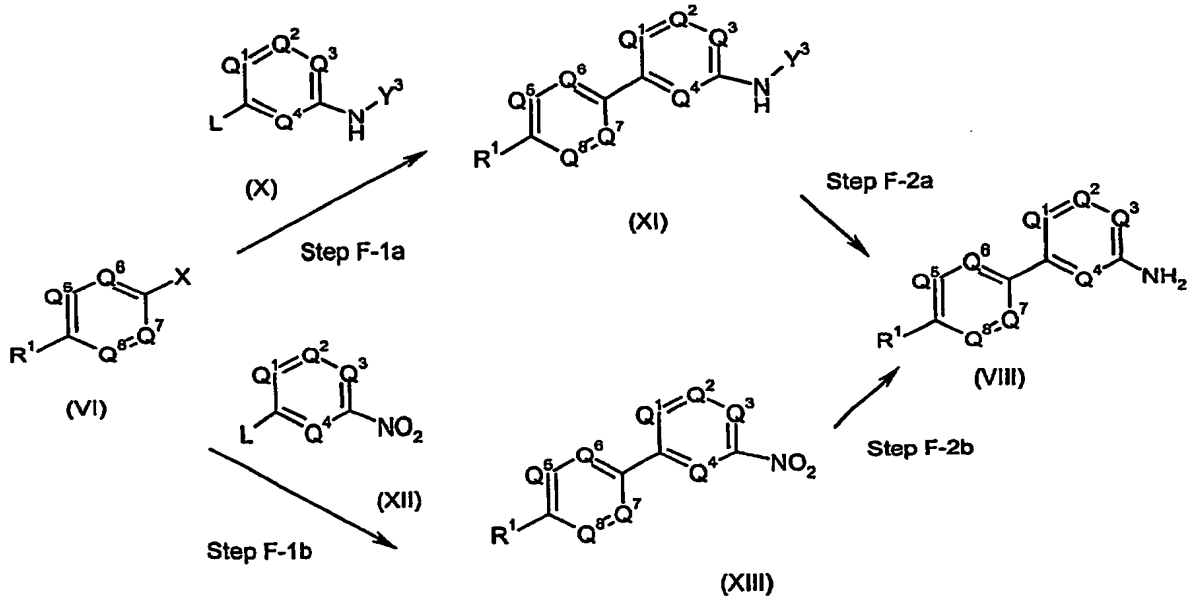
The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimeth-

oxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methyl-pyrrolidone; alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; organic acid such as acetic acid; water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

Preparation of the compound of the formula (VIII)

Method [F]



The compound of the formula (VIII) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8 and R^1 are the same as defined above) can be obtained by the following procedures;

Step F-1a : The compound of the formula (XI) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8 and R^1 are the same as defined above and Y^3 represents a protecting group of

amine including, for instance, tert-butoxycarbonyl and 9-fluorenylmethoxycarbonyl) can be obtained by the reaction of the compound of the formula (VI) (wherein Q^5, Q^6, Q^7, Q^8, R^1 and X are the same as defined above) with the compound of the formula (X) (wherein Q^1, Q^2, Q^3, Q^4, L and Y^3 are the same as defined above) in a similar manner described in Step C-2 of Method [C] for the preparation of the compound of the formula (II).

Step F-2a : The compound of the formula (VIII) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8 and R^1 are the same as defined above) can be obtained by the removal of a protecting group of the compound of the formula (XI) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^1 and $Y^3$are the same as defined above).

The removal of protective group Y_3 can be done by using a reagent including, for instance, an acid such as trifluoroacetic acid, or a base such as morpholine.

The reaction may be carried out without solvent or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 60 hours and preferably 1 to 48 hours.

The compound of the formula (VIII) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8 and R^1 are the same as defined above) can also be obtained by the following procedures;

Step F-1b : The compound of the formula (XIII) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8 and R^1 are the same as defined above) can be obtained by the reaction of the compound of the formula (VI) (wherein Q^5, Q^6, Q^7, Q^8, R^1 and X are the same as defined above) with the compound of the formula (XII) (wherein Q^1, Q^2, Q^3, Q^4, and L are the same as defined above) in a similar manner described in Step C-2 of Method [C] for the preparation of the compound of the formula (II).

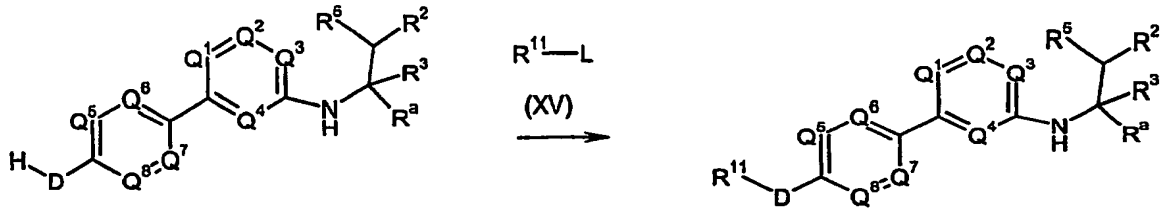
Step F-2b : The compound of the formula (VIII) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8 and R^1 are the same as defined above) can be obtained by the reduction of nitro group of compound of the formula (XIII) (wherein Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8 and R^1 are the same as defined above) using an agent including, for instance, metals such as zinc and iron in the presence of acid including, for instance, hydrochloric acid and acetic acid and stannous chloride, or by hydrogenation using a catalyst including, for instance, palladium on carbon and platinum on carbon.

The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxy-ethane, aromatic hydrocarbons such as benzene, toluene and xylene, alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, water and others.

The reaction may be carried out, usually, at room temperature to 100 °C for 30 minutes to 12 hours.

The compound of the formula (X) and (XII) are commercially available or can be prepared by the use of known techniques.

Method [G]



(XIV) (II")

The compound of the formula (II") (wherein D, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^2, R^3, R^5 and R^{11} are the same as defined above and D represents O, S or NH) can be obtained by the reaction of the compound of the formula (XIV) (wherein D, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^2, R^3, and R^5 are the same as defined above) with the compound of the formula (XV) (wherein R^{11} and L are the same as defined above).

The reaction may be carried out in a solvent including, for instance, alcohols such as methanol and ethanol; ethers, such as dioxane, and tetrahydrofuran (THF); nitriles such as acetonitrile; amides such as dimethylformamide (DMF) and dimethyl-acetamide; sulfoxides such as dimethyl sulfoxide, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

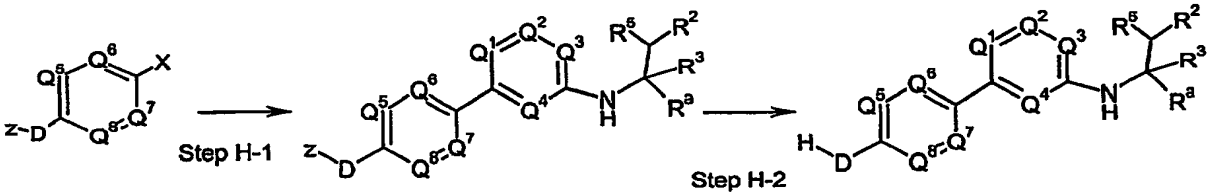
The reaction temperature of the reaction can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about -10°C to 200°C and preferably about 10°C to 80°C. The reaction may be carried out for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The reaction can be advantageously conducted in the presence of a base. Examples of the base include an alkali metal hydride such as sodium hydride or potassium hydride; alkali metal alkoxide such as sodium methoxide or sodium ethoxide; alkali metal hydroxide such as sodium hydroxide or potassium hydroxide; carbonates such as sodium carbonate or potassium carbonate, and hydrogen carbonates such as

sodium hydrogen carbonate and potassium hydrogen carbonate; organic amines such as triethylamine.

Preparation of the compound of the formula (XIV)

Method [H]



(XVI) (XVII) (XIV)

The compound of the formula (IX) (wherein D, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^2, R^3, and R^5 are the same as defined above) can be obtained by following steps;

Step H-1: The compound of the formula (XVII) (wherein D, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^2, R^3, and R^5 are the same as defined above and Z represents protecting groups such as oxygen- protecting group; for instance, C_{1-6} alkyl, benzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl and the like, sulfur-protecting group; for instance, acetyl, benzoyl and the like, and amino- protecting group; for instance, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl and the like) can be obtained in a similar manner described in Method [A]-[F] for the preparation of the compound of the formula (II) or (II') by using the compound of the formula (XVI) (wherein D, Q^5, Q^6, Q^7, Q^8, X and Z are the same as defined above) instead of the compound of the formula (VI).

Step H-2: The compound of the formula (XIV) (wherein D, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^2, R^3, and R^5 are the same as defined above) can be prepared by the removal of protective group Z of the compound of the formula (XVII) (wherein D, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, R^a, R^2, R^3, R^5 and Z are the same as defined above).

When D refers to oxygen, the removal of protective group Z can be conducted by using a base including, for instance, sodium hydroxide, lithium hydroxide and potassium hydroxide, or an acid including, for instance, hydrochloric acid, trifluoroacetic acid and BBr_3. The deprotection can also be done by hydrogenation using a catalyst including, for instance, palladium on carbon and palladium hydroxide, when Z is benzyl , 4-methoxybenzyl or 3,4-dimethoxybenzyl.

When D refers to sulfur, the removal of protective group Z can be conducted by using a base such as sodium hydroxide, lithium hydroxide, potassium hydroxide, and the like.

When D refers to amino, the removal of protective group Z can be conducted by using acids such as trifluoroacetic acid, hydrochloric acid, and the like.

The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; dimethylformamide (DMF), dimethylacetamide(DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 0°C to 200°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

The compound of the formula (XVI) is commercially available or can be prepared by the use of known techniques.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, successively.

Acids to form salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders,

granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions.

They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form

of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxy-methyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable

carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01 mg/kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100 mg/kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Examples

The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the meets and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Melting points are uncorrected. Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column (4.6 mm x 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate. Mass spectra were obtained using electrospray (ES) ionization techniques (micromass Platform LC). TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Great Britain, Tokyo kasei kogyo Co., Ltd., Japan, Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Great Britain, Merck KgaA, Germany, Kanto Chemical Co., Ltd. ^{1}H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ^{1}H) spectrometer or Brucker 500 UltraShieled™ (500 MHz for 1H) . Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doblet, triplet, quartet, multiplet, and broad, respectively. The mass determinations were carried out by MAT95 (Finnigan MAT).

The effects of the present compounds were examined by the following assays and pharmacological tests.

[Measurement of the [^{3}H]-iloprost binding to HEL cells] (Assay 1)

A human erythloleukemia cell line, HEL 92.1.7, was purchased from American Type Culture Correction and maintained in RPMI-1640 medium (Gibco BRL) supplemented with 10% fetal calf serum (FCS), 2 mM glutamine, 4.5 g/L glucose, 10 mM Hepes, 1 mM sodium pyruvate, 100 U/ml penicillin, and 100 μg/ml streptomycin in a humidified 5% CO_2 atmosphere at 37°C. Cells were collected with centrifugation and washed with binding assay buffer (BAB: 50 mM Tris-HCl, 5 mM $MgCl_2$ (pH 7.5)). Cells were suspended at the density of 6.25 x 10^6 cells/ml in BAB, and one million cells in 160 μl aliquot of cell suspension were put in a well of 96 well plate (Falcon). Then, 20 μl of compound solution, 100 μM of iloprost (for non-specific binding), or buffer alone (total binding), diluted with 1% DMSO in BAB was added. Finally, another 20 μl containing [^{3}H]-iloprost (0.02 μCi, 0.5-1 pmol) in BAB was added and incubated at room temperature for 30 min with a gentle shaking. Cell suspension was then transferred to a well of MultiScreen plate with GF/C glass filters (Millipore) to harvest cells. Cells were washed twice with 200 μl of ice-cold BAB and the plate was kept at 55°C for 30 min to dry filters. The filter in the well was punched out to a counting tube and 2 ml of Ultima Gold XR (Packard) was added. [^{3}H]-radio activity in the filter was measured by a liquid scintillation counter (Beckman, USA).

[Iloprost-induced cAMP production assay in HEL cells] (Assay 2)

HEL cells were collected with centrifugation and washed with cAMP assay buffer (CAB: Hank's balanced salt solution, 17 mM Hepes, 0.1% bovine serum albumin, 1 mM IBMX, 0.4% DMSO, and 1 mM L-ascorbic acid sodium salt (pH 7.4)). Cells were suspended at the density of 2.5 x 10^5 cells/ml in CAB, and twenty thousand cells in 80 μl aliquot of cell suspension were put in a well of 96 well plate (Falcon). Then, 10 μl of compound solution diluted with 1% DMSO in CAB or buffer alone was added. The plate was incubated at 37°C for 30 min. Then, another 10 μl containing 100 nM iloprost in CAB or buffer alone was added and further incubated

at 37°C for 30 min. cAMP content in the well was measured by a cAMP ELISA kit (Applied Biosystems, USA).

[Measurement of rhythmic bladder contraction in anesthetized rats]

(1) Animals

Female Sprague-Dawley rats (200~250 g / Charles River Japan) were used.

(2) Rhythmic bladder contraction in anesthetized rats

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.25 g/kg. The trachea was cannulated with a polyethylene tube (HIBIKI, No.8) to facilitate respiration; and a cannula (BECTON DICKINSON, PE-50) was placed in the left femoral vein for intravenous administration of testing compounds. The abdomen was opened through a midline incision, and after both ureters were cut, a water-filled balloon (about 1 ml capacity) was inserted through the apex of the bladder dome. The balloon was connected to a pressure transducer onto a polygraph. Rhythmic bladder contraction was elicited by raising up intravesical pressure to approximately 15 cm H_2O. After the rhythmic bladder contraction was stable, a testing compound was administered intravenously. Activity was estimated by measuring disappearance time and amplitude of the rhythmic bladder contraction. The effect on amplitude of bladder contractions was expressed as a percent suppression of the amplitude of those after the disappearance was recovered. Experimental values were expressed as the mean±S.E.M. The testing compounds–mediated inhibition of the rhythmic bladder contraction was evaluated using Student's t-test. A probability level less than 5% was accepted as significant difference.

Results of IP receptor binding/cAMP is shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase

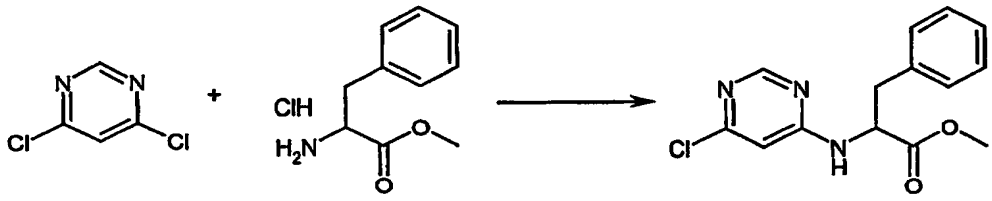
synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in three classes of activity as follows:

IC_{50} = A <0.1 μM ≤B <1 μM ≤ C

The compounds of the present invention also show excellent selectivity, and strong activity in vivo assays.

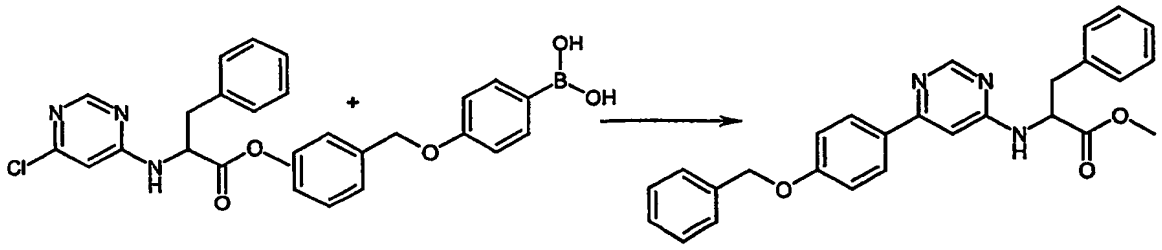
Example 1-1

Methyl *N*-(6-chloro-4-pyrimidinyl)phenylalaninate



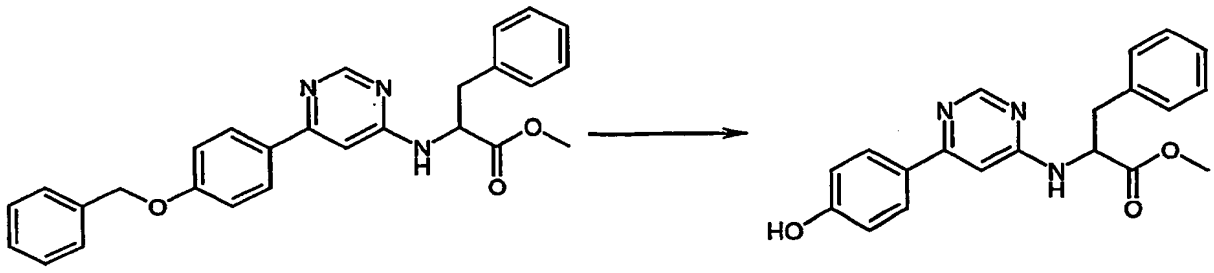
To a mixture of 4,6-dichloropyrimidine (0.500 g, 3.356 mmol), DL-phenylalanine methyl ester hydrochloride (0.796 g, 3.692 mmol) and ethanol (15 mL) was added *N,N*-diisopropylethylamine (1.228 mL, 7.048 mmol), and the mixture was stirred at reflux for 2 hours. After cooled to room temperature, the mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel (hexane: ethyl acetate, 3:1) to give methyl *N*-(6-chloro-4-pyrimidinyl)phenylalaninate (0.497 g, 51%) as a colorless oil.

Methyl *N*-{6-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate



To a mixture of methyl *N*-(6-chloro-4-pyrimidinyl)phenylalaninate (0.192 g, 0.658 mmol), 4-(benzyloxy)phenylboronic acid (0.150 g, 0.658 mmol) and DMF (3 mL) under an argon atmosphere was added 2N sodium carbonate aqueous solution (0.975 mL, 1.95 mmol) followed by tetrakis(triphenylphosphine)palladium (0.038 g, 0.033 mmol). The mixture was stirred at 100°C overnight. After cooled to room temperature, the mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel (hexane: ethyl acetate, 2:1) to give methyl *N*-{6-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate (0.028 g, 10%) as a colorless oil.

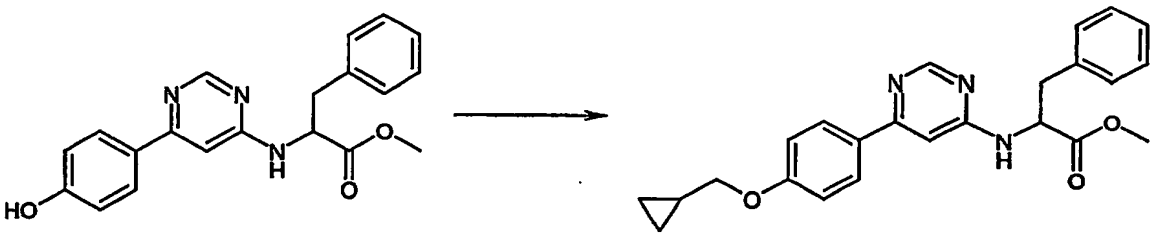
Methyl *N*-[6-(4-hydroxyphenyl)-4-pyrimidinyl]phenylalaninate



A mixture of methyl *N*-{6-[4-(benzyloxy)phenyl]-4-pyrimidinyl}phenylalaninate (0.253 g, 0.576 mmol), 10% palladium on activated carbon (0.050 g) and methanol (10 mL) under a hydrogen atmosphere was stirred at room temperature for 2 days. The resulting mixture was filtered through a Celite pad, and the filtrate was

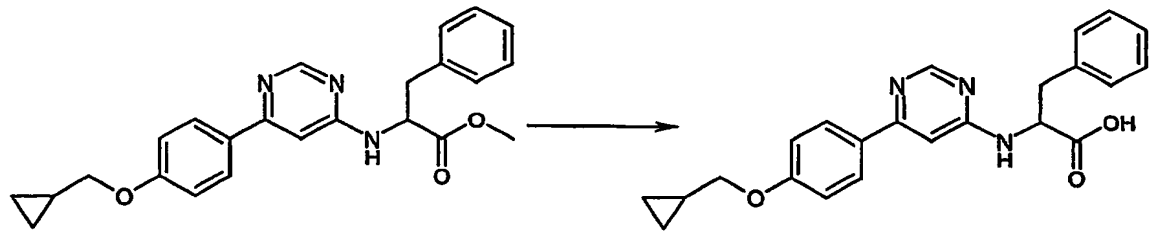
concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (hexane: ethyl acetate, 1:1) to give methyl *N*-[6-(4-hydroxyphenyl)-4-pyrimidinyl]phenylalaninate (0.150 g, 75%) as a colorless oil.

Methyl *N*-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}phenylalaninate



To a mixture of methyl *N*-[6-(4-hydroxyphenyl)-4-pyrimidinyl]phenylalaninate (0.020 g, 0.057 mmol), potassium carbonate (0.016 g, 0.11 mmol), acetone (1.0 mL) and DMF (1.0 mL) was added (bromomethyl)cyclopropane (0.008 mL, 0.09 mmol), and the mixture was stirred at reflux overnight. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparaive TLC (hexane: ethyl acetate, 1:1) to give Methyl *N*-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}phenylalaninate (0.024 g, 100%) as an yellow oil.

N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine



A mixture of Methyl *N*-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}phenylalaninate (0.024 g, 0.059 mmol), 1M NaOH aqueous solution (0.5 mL) and methanol (2.0 mL) was stirred at room temperature overnight. After removal of methanol

under reduced pressure, the residue was diluted with water. The solution was washed with diethyl ether and acidified by 1M aqueous hydrochloric acid. The resulting precipitaite was collected by filteration and washed with ethyl acetate to give *N*-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine (0.018 g, 77%) as a colorless solid.

Melting point: 216-218°C

Molecular weight: 389.45

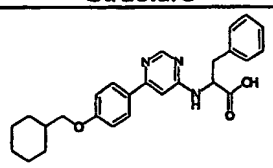
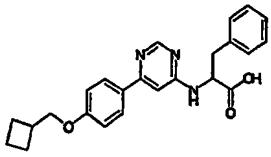
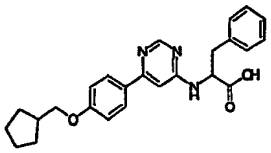
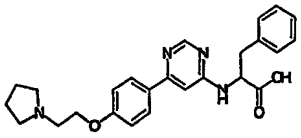
Mass spectrometry: 390 $(M + H)^+$

In vitro activity grade: A

^{1}H-NMR (500 MHz, MeOH-*d4*): δ 0.38(2H, m), 0.64 (2H, m), 1.28 (1H, m), 3.12 (1H, dd, J = 9.1, 13.9 Hz), 3.42 (1H, dd, J = 4.7, 13.6 Hz), 3.92 (2H, d, J = 6.9 Hz), 5.21 (1H, m), 6.96 (1H, s), 7.12 (2H, d, J = 8.8 Hz), 7.21 (1H, m), 7.26 (4H, m), 7.73 (2H, d, J = 8.5 Hz), 8.58 (1H, s).

Examples 1-2 to 1-5

According to the similar synthetic procedure of Example 1-1, or Method [A]-[H], compounds shown in Table 1 were prepared.

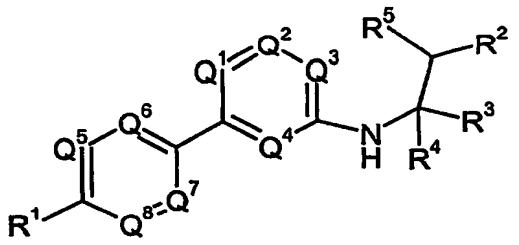
Ex No	Structure	Mol weight	MP	In vitro
1-2		431,54	118-120	A
1-3		403,49	210-213 (dec.	A
1-4		417,51	125-128	A
1-5		432,53	117-120	C

According to the similar synthetic procedure of Example 1-1, or Method or Method [A]-[H], the following compounds can be prepared.

N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}-4-fluorophenylalanine;
N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}-N-[2-phenyl-1-(1H-tetra-azol-5-yl)ethyl]amine;
N-{6-[4-(cyclopropylmethoxy)-2-fluorophenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopropylmethoxy)-3-fluorophenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopropylmethoxy)phenyl]-5-fluoro-4-pyrimidinyl}phenylalanine;
and
N-{6-[4-(cyclohexylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine.

Claims

(1) An phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

wherein

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, $Q^7$and Q^8 independently represent CH, CR^{10} or N,

wherein

R^{10} represents halogen;

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NHR^{11}$, or $-CH_2R^{11}$,

wherein

R^{11} represents (C_{1-6}) alkyl substituted by a 3-8 membered saturated ring optionally having one or two N, (C_{2-6})alkenyl substituted by a 3-8 membered saturated ring optionally having one or two N, or (C_{2-6})alkynyl optionally substituted by a 3-8 membered saturated ring optionally having one or two N;

R^2 represents hydrogen, hydroxy, halogen, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by -mono, -di or -tri halogen, amino, (C_{1-6})alkylamino, aryl or a 5 or 6

membered heteroaryl containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said aryl and heteroaryl are optionally having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, $di(C_{1-6})$ alkylamino, phenyl and a 5 or 6 membered heteroaryl containing 1-4 heteroatoms selected from the group of O, N, and S,

wherein

said phenyl and heteroaryl optionally are having one or more substituents selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, $N(C_{1-6})$ alkylamino, and $di(C_{1-6})$ alkylamino;

R^3 represents hydrogen, or C_{1-6} alkyl optionally substituted -mono, -di or -tri halogen;

R^4 represents carboxy or tetrazolyl; and

R^5 represents hydrogen, hydroxy, C_{1-6} alkyl, or C_{1-6} alkoxy.

(2) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

(3) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^3 and Q^4 represent N;

Q^1, Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

(4) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1 and Q^4 represent N;

Q^2, Q^3, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

(5) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH; and

R^4 represents carboxy.

(6) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1, Q^3 and Q^8 represent N;

Q^2, Q^4, Q^5, Q^6 and Q^7 represent CH; and

R^4 represents carboxy.

(7) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^3, Q^4 and Q^8 represent N;

Q^1, Q^2, Q^5, Q^6 and Q^7 represent CH; and

R^4 represents carboxy.

(8) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1 and Q^3 represent N;

Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH;

Q^4 represent CR^{10},

wherein

R^{10} represents halogen; and

R^4 represents carboxy.

(9) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^7 and Q^8 represent CH;

Q^6 represents CR^{10},

wherein

R^{10} represents halogen; and

R^4 represents carboxy.

(10) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^6 and Q^7 represent CH;

Q^5 and Q^8 independently represent CH or CR^{10},

wherein

R^{10} represents halogen; and

R^4 represents carboxy.

(11) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

(12) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^3 and Q^4 represent N;

Q^1, Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

(13) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1 and Q^4 represent N;

Q^2, Q^3, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

(14) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7 and Q^8 represent CH;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of

halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

(15) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1 and Q^3 represent N;

Q^2, Q^5, Q^6, Q^7 and Q^8 represent CH;

Q^4 represents C R^{10},

wherein

R^{10} represents fluoro or chloro;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

(16) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^6 and Q^7 represent CH;

Q^5 and Q^8 independently represent CH or CR^{10},

wherein

R^{10} represents fluoro or chloro;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

(17) The phenyl or heteroaryl amino alkane derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

Q^1 and Q^3 represent N;

Q^2, Q^4, Q^5 and Q^8 represent CH;

Q^6 and Q^7 independently represent CH or CR^{10},

wherein

R^{10} represents fluoro or chloro;

R^1 represents (C_{1-6})alkoxy substituted by a (C_{3-7})cycloalkyl;

R^2 represents halogen, hydroxy, (C_{3-7})cycloalkyl, or phenyl optionally having one to three substituents selected from the group consisting of halogen, hydroxy, amino, (C_{1-6})alkylamino, and phenyl optionally substituted by halogen, hydroxy or amino;

R^3 represents hydrogen;

R^4 represents carboxy; and

R^5 represents hydrogen.

(18) The phenyl or heteroaryl amino alkane derivative, its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said derivative is selected from the group consisting of the following compounds:

N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}-4-fluorophenylalanine;
N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopropylmethoxy)phenyl]-4-pyrimidinyl}-N-[2-phenyl-1-(1H-tetraazol-5-yl)ethyl]amine;
N-{6-[4-(cyclopropylmethoxy)-2-fluorophenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopropylmethoxy)-3-fluorophenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopropylmethoxy)phenyl]-5-fluoro-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclohexylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclobutylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine;
N-{6-[4-(cyclopentylmethoxy)phenyl]-4-pyrimidinyl}phenylalanine;and
N-(6-{4-[2-(1-pyrrolidinyl)ethoxy]phenyl}-4-pyrimidinyl)phenylalanine.

(19) A medicament comprising the phenyl or heteroaryl amino alkane derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(20) The medicament as claimed in claim 19, further comprising one or more pharmaceutically acceptable excipients.

(21) The medicament as claimed in claim 19, wherein the phenyl or heteroaryl amino alkane derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is an IP receptor antagonist.

(22) The medicament as claimed in claim 19 for prophylaxis and/or treatment of urological disorder or disease.

(23) The medicament as claimed in claim 19 for prophylaxis and/or treatment of pain.

(24) The medicament as claimed in claim 19 for prophylaxis and/or treatment of hypotension.

(25) The medicament as claimed in claim 19 for prophylaxis and/or treatment of hemophilia and hemorrhage.

(26) The medicament as claimed in claim 19 for prophylaxis and/or treatment of inflammation.

(27) Use of compounds according to Claims 1 for manufacturing a medicament for the treatment and/or prophylaxis of urological disorders.

(28) Use of compounds according to Claims 1 for manufacturing a medicament for the treatment and/or prophylaxis of pain.

(29) Use of compounds according to Claims 1 for manufacturing a medicament for the treatment and/or prophylaxis of hypotension.

(30) Use of compounds according to Claims 1 for manufacturing a medicament for the treatment and/or prophylaxis of hemophilia and hemorrhage.

(31) Use of compounds according to Claims 1 for manufacturing a medicament for the treatment and/or prophylaxis of inflammation.

(32) Process for controlling urological disorders in humans and animals by administration of an IP receptor-antagonisticly effective amount of at least one compound according to claims 1.

Phenyl or heteroaryl amino alkane derivatives

ABSTRACT

The present invention relates to a phenyl or heteroaryl amino alkane derivatives which are useful as an active ingredient of pharmaceutical preparations. The phenyl or heteroaryl amino alkanes of the present invention have IP receptor antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with IP receptor antagonistic activity.

Such diseases include urological diseases or disorder as follows: bladder outlet obstruction, overactive bladder, urinary incontinence, detrusor hyper-reflexia, detrusor instability, reduced bladder capacity, frequency of micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benighn prostatic hypertrophy (BPH), prostatitis, urinary frequency, nocturia, urinary urgency, pelvic hypersensitivity, urethritis, pelvic pain syndrome, prostatodynia, cystitis, or idiophatic bladder hypersensitivity.

The compounds of the present invention are also useful for treatment of pain including, but not limited to inflammatory pain, neuropathic pain, acute pain, chronic pain, dental pain, premenstrual pain, visceral pain, headaches, and the like; hypotension; hemophilia and hemorrhage; and inflammation, since the diseases also is alleviated by treatment with an IP receptor antagonist.